(FILE 'HOME' ENTERED AT 12:03:49 ON 09 NOV 2001)

FILE 'MEDLINE, CAPLUS' ENTERED AT 12:04:08 ON 09 NOV 2001
L1 4320 S (HEDGEHOG OR IHH OR SHH)
L2 186 S L1 (P)(ADMINIST? OR DOSE OR DOSES OR DOSING)
L3 108 S L2 NOT PY>1997

FILE 'STNGUIDE' ENTERED AT 12:13:41 ON 09 NOV 2001

FILE 'MEDLINE, CAPLUS' ENTERED AT 12:19:50 ON 09 NOV 2001

FILE 'STNGUIDE' ENTERED AT 12:19:51 ON 09 NOV 2001

FILE 'MEDLINE, CAPLUS' ENTERED AT 12:24:27 ON 09 NOV 2001

FILE 'STNGUIDE' ENTERED AT 12:24:33 ON 09 NOV 2001

FILE 'MEDLINE' ENTERED AT 12:41:01 ON 09 NOV 2001
L4 3 S (HEMATOP? OR HEAMATOP?) (15W) (HEDGEHOG OR IHH OR SHH OR DHH)

FILE 'STNGUIDE' ENTERED AT 12:43:32 ON 09 NOV 2001

FILE 'MEDLINE' ENTERED AT 12:50:38 ON 09 NOV 2001

FILE 'STNGUIDE' ENTERED AT 12:50:38 ON 09 NOV 2001

FILE 'MEDLINE' ENTERED AT 12:50:44 ON 09 NOV 2001

FILE 'STNGUIDE' ENTERED AT 12:50:45 ON 09 NOV 2001

L4 ANSWER 1 OF 3 MEDLINE

AB During gastrulation in the mouse, mesoderm is induced and patterned by secreted signaling molecules, giving rise first to primitive erythroblasts and vascular endothelial cells. We have demonstrated previously that development of these lineages requires a signal(s) secreted from the adjacent primitive endoderm. We now show that Indian hedgehog (Ihh) is a primitive endoderm-secreted signal that alone is sufficient to induce formation of **hematopoietic** and endothelial cells. Strikingly, as seen with primitive endoderm, **Ihh** can respecify prospective neural ectoderm (anterior epiblast) along **hematopoietic** and endothelial (posterior) lineages. Downstream targets of the **hedgehog** signaling pathway (the genes encoding patched, smoothened and Gli1) are upregulated in anterior epiblasts cultured in the presence of Ihh protein, as is Bmp4, which may mediate the effects of Ihh. Blocking Ihh function in primitive endoderm inhibits activation of **hematopoiesis** and vasculogenesis in the adjacent epiblast, suggesting that **Ihh** is an endogenous signal that plays a key role in the development of the earliest hemato-vascular system. To our knowledge, these are the earliest functions for a hedgehog protein in post-implantation development in the mouse embryo.

=> d ti, au, so
YOU HAVE REQUESTED DATA FROM FILE 'MEDLINE' - CONTINUE? (Y)/N:y

L4 ANSWER 1 OF 3 MEDLINE

TI Indian hedgehog activates hematopoiesis and vasculogenesis and can respecify prospective neurectodermal cell fate in the mouse embryo.

AU Dyer M A; Farrington S M; Mohn D; Munday J R; Baron M H

SO DEVELOPMENT, (2001 May) 128 (10) 1717-30.
Journal code: ECW; 8701744. ISSN: 0950-1991.

L3 ANSWER 2 OF 108 MEDLINE
TI Relationship between **dose**, distance and time in Sonic **Hedgehog**-mediated regulation of anteroposterior polarity in the chick limb.
AU Yang Y; Drossopoulou G; Chuang P T; Duprez D; Marti E; Bumcrot D; Vargesson N; Clarke J; Niswander L; McMahon A; Tickle C
SO DEVELOPMENT, (1997 Nov) 124 (21) 4393-404.
Journal code: ECW; 8701744. ISSN: 0950-1991.
AB Anteroposterior polarity in the vertebrate limb is thought to be regulated in response to signals derived from a specialized region of distal posterior mesenchyme, the zone of polarizing activity. Sonic **Hedgehog** (**Shh**) is expressed in the zone of polarizing activity and appears to mediate the action of the zone of polarizing activity. Here we have manipulated **Shh** signal in the limb to assess whether it acts as a long-range signal to directly pattern all the digits. Firstly, we demonstrate that alterations in digit development are dependent upon the **dose** of **Shh** applied. DiI-labeling experiments indicate that cells giving rise to the extra digits lie within a 300 microm radius of a **Shh** bead and that the most posterior digits come from cells that lie very close to the bead. A response to **Shh** involves a 12-16 hour period in which no irreversible changes in digit pattern occur. Increasing the time of exposure to **Shh** leads to specification of additional digits, firstly digit 2, then 3, then 4. Cell marking experiments demonstrate that cells giving rise to posterior digits are first specified as anterior digits and later adopt a more posterior character. To monitor the direct range of **Shh** signalling, we developed sensitive assays for localizing **Shh** by attaching alkaline phosphatase to **Shh** and introducing cells expressing these forms into the limb bud. These experiments demonstrate that long-range diffusion across the anteroposterior axis of the limb is possible. However, despite a dramatic difference in their diffusibility in the limb mesenchyme, the two forms of alkaline phosphatase-tagged **Shh** proteins share similar polarizing activity. Moreover, **Shh**-N (aminoterminal peptide of **Shh**)-coated beads and **Shh**-expressing cells also exhibit similar patterning activity despite a significant difference in the diffusibility of **Shh** from these two sources. Finally, we demonstrate that when **Shh**-N is attached to an integral membrane protein, cells transfected with this anchored signal also induce mirror-image pattern duplications in a **dose**-dependent fashion similar to the zone of polarizing activity itself. These data suggest that it is unlikely that **Shh** itself signals digit formation at a distance. Beads soaked in **Shh**-N do not induce **Shh** in anterior limb mesenchyme ruling out direct propagation of a **Shh** signal. However, **Shh** induces **dose**-dependent expression of Bmp genes in anterior mesenchyme at the start of the promotion phase. Taken together, these results argue that the **dose**-dependent effects of **Shh** in the regulation of anteroposterior pattern in the limb may be mediated by some other signal(s). BMPs are plausible candidates.

L3 ANSWER 23 OF 108 MEDLINE
TI Requirement of 19K form of Sonic hedgehog for induction of distinct ventral cell types in CNS explants.
AU Marti E; Bumcrot D A; Takada R; McMahon A P
SO NATURE, (1995 May 25) 375 (6529) 322-5.
Journal code: NSC; 0410462. ISSN: 0028-0836.
AB The identity and patterning of ventral cell types in the vertebrate central nervous system depends on cell interactions. For example, induction of a specialized population of ventral midline cells, the floor plate, appears to require contact-mediated signalling by the underlying

notochord, whereas diffusible signals from the notochord and floor plate can induce ventrolaterally positioned motor neurons. Sonic **hedgehog** (**Shh**), a vertebrate **hedgehog**-family member, is processed to generate two peptides (M(r) 19K and 26/27K) which are secreted by both of these organizing centres. Moreover, experiments in a variety of vertebrate embryos, and in neural explants in vitro, indicate that **Shh** can mediate floor-plate induction. Here we have applied recombinant **Shh** peptides to neural explants in serum-free conditions. High concentrations of **Shh** bound to a matrix induce floor plate and motor neurons, and addition of **Shh** to the medium leads to **dose**-dependent induction of motor neurons. All inducing activity resides in a highly conserved amino-terminal peptide (M(r) 19K). Moreover, antibodies that specifically recognize this peptide block induction of motor neurons by the notochord. We propose that **Shh** acts as a morphogen to induce distinct ventral cell types in the vertebrate central nervous system.

L3 ANSWER 24 OF 108 MEDLINE
TI Relationship between retinoic acid and sonic hedgehog, two polarizing signals in the chick wing bud.
AU Helms J; Thaller C; Eichele G
SO DEVELOPMENT, (1994 Nov) 120 (11) 3267-74.
Journal code: ECW; 8701744. ISSN: 0950-1991.
AB Local application of all-trans-retinoic acid (RA) to the anterior margin of chick limb buds results in pattern duplications reminescent of those that develop after grafting cells from the zone of polarizing activity (ZPA). RA may act directly by conferring positional information to limb bud cells, or it may act indirectly by creating a polarizing region in the tissue distal to the RA source. Here we demonstrate that tissue distal to an RA-releasing bead acquires polarizing activity in a **dose**-dependent manner. Treatments with pharmacological (beads soaked in 330 micrograms/ml) and physiological (beads soaked in 10 micrograms/ml) **doses** of RA are equally capable of inducing digit pattern duplication. Additionally, both treatments induce sonic **hedgehog** (**shh**; also known as vertebrate **hedgehog**-1, vhh-1), a putative ZPA morphogen and Hoxd-11, a gene induced by the polarizing signal. However, tissue transplantation assays reveal that pharmacological, but not physiological, **doses** create a polarizing region. This differential response could be explained if physiological **doses** induced less **shh** than pharmacological **doses**. However, our in situ hybridization analyses demonstrate that both treatments result in similar amounts of mRNA encoding this candidate ZPA morphogen. We outline a model describing the apparently disparate effects of pharmacologic and physiological **doses** RA on limb bud tissue.

L3 ANSWER 82 OF 108 CAPLUS COPYRIGHT 2001 ACS
TI Induction of midbrain dopaminergic neurons by Sonic hedgehog
AU Hynes, Mary; Porter, Jeffery A.; Chiang, Chin; Chang, David; Tessier-Lavigne, Marc; Beachy, Philip A.; Rosenthal, Arnon
SO Neuron (1995), 15(1), 35-44
CODEN: NERNET; ISSN: 0896-6273
AB Midbrain dopaminergic neurons, whose loss in adults results in Parkinson's disease, can be specified during embryonic development by a contact-dependent signal from floor plate cells. Here the authors show that the amino-terminal product of Sonic **hedgehog** autoproteolysis (**SHH**-N), an inductive signal expressed by floor plate cells, can induce dopaminergic neurons in vitro. The authors show further that manipulations to increase the activity of cAMP-dependent protein kinase A, which is known to antagonize **hedgehog** signaling, can block dopaminergic neuron induction by floor plate cells. The results and those of other studies indicate that **SHH**-N can

function in a dose-dependent manner to induce different cell types within the neural tube. The results also provide the basis for a potential cell transplantation therapy for Parkinson's disease.